

Penicillin hypersensitivity : mechanism, diagnosis and management

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The penicillins form a major and widely used group of antibacterial antibiotics. In extensive clinical use at normal dose regimens and even under circumstances of extremely high cumulative dose, the penicillins have a very low intrinsic pharmacotoxicological profile. The major adverse effect associated with their use is the development in susceptible individuals, of allergic reactions.

A relatively high incidence of urticaria and other allergic reactions was noted soon after the introduction of penicillins, but the role played by the penicillin moiety itself, compared with excipients and oily suspension vehicles was not clear at that time. Topical application of penicillins to the skin was associated, not only with concern over the development of bacterial resistance, but also with a recorded 5 to 10 per cent incidence of allergic sensitisation¹ and is now largely discouraged.

The range of penicillins available for clinical use is extensive. This review addresses questions on the mechanisms of immunogenicity, allergenicity and cross reactivity of the penicillins and describes

the most important clinical syndromes and their management.

Incidence

Several factors militate against the establishment of true incidence figures for penicillin allergy. (1) It is not always possible to demonstrate a causal relationship between the adverse event and drug administration especially in a seriously ill patient, a problem compounded by multi-drug therapy. (2) The reputation that penicillins have as drug allergens means that they are more likely to be implicated as the cause of a patient's allergic-like reaction even if the patient is also receiving other drugs. (3) Diagnostic procedures for penicillin and other drug allergies are less than adequate making it difficult to distinguish true allergy from other syndromes.

Nonetheless, several surveys have been carried out. A widely quoted world survey by Idsoe *et al*² reported a frequency of allergic reactions to penicillin of 0.7 to 10 per cent of treated patients. Anaphylactic type reactions occurred in 0.004 to 0.015 per cent of treated patients with fatalities from shock ranging from 0.0015

to 0.002 per cent. Of particular interest to the pediatrician was a detailed analysis of 151 reported deaths which showed that ten subjects were aged less than 5 years and two were only 3 months old.

Basic mechanisms

The penicillins, in common with most drugs, are molecules of low molecular weight within the 350 to 770 daltons range. As such they are too small to take part in the normal immunological reactions which involve recognition of foreign materials, initiation of immunological events such as generation of memory cells and synthesis of specific antibody. However, it is clear that the penicillins and some other drugs and low molecular weight chemicals can cause allergic reactions in some individuals. The work of Landsteiner and Jacobs³ suggested an answer to this paradox using a model system. In a study which involved the evaluation of a number of chlorinated nitrobenzenes, they showed correlation between the ability to react with the amino group of aniline and the development of contact sensitisation in the guinea pig. These initial studies led to generalisation of the findings, to form the basis of the hapten theory of drug immunogenicity. This states that for a low molecular weight compound to initiate an immune response it must be capable of forming a covalent bond with macromolecules.

Many studies have shown that the penicillins can react under physiological conditions with protein amino groups to form a stable penicilloyl group (Fig 1). Reaction occurs between a protein amino group and the β -lactam ring carbonyl of the penicillin, resulting in the cleavage of

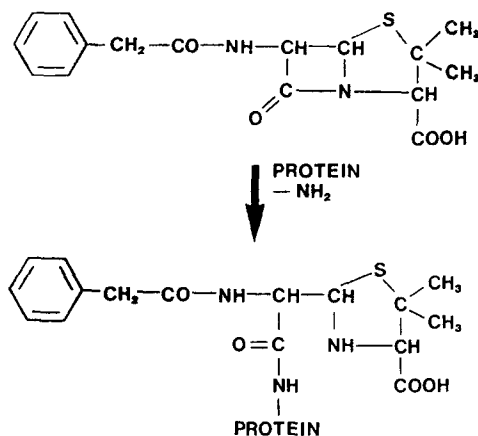


Fig. 1. Formation of the benzyl penicilloyl determinant by reaction of benzyl penicillin with protein amino groups.

this ring and loss of antibiotic activity. Studies in man and animals have shown that the predominating immunological response is directed against the penicilloyl group, and for this reason it is termed the major determinant of penicillin allergy. Some breakdown products of penicillins can also react with protein to give other haptenic groups (see Dewdney⁵ and references therein). These other determinants are collectively called the minor determinants, although for some allergic subjects they represent the major cause of symptoms. Other individuals show very heterogeneous responses involving major and minor determinants.

It is now known that the total antigenic and possibly also allergenic potential of a penicillin may be enhanced by the presence of low but variable amounts of other extrinsic, but penicillin related materials. These are penicilloylated proteins and polymeric forms potentially capable of eliciting allergic reactions in sensitive individuals, without the need

for prior conjugation to a host macromolecule.

Controversy continues to exist over the presence and significance of penicilloylated proteins,^{6,7} but it seems likely that at the levels now present in penicillins they are of only limited importance. The clinical significance of polymers in penicillin has not been formally established.

Clinical syndromes

A number of distinct clinical syndromes has been recognised to be associated with penicillin induced allergy. It is possible to classify these mechanistically in terms of postulated immunological etiology.

(1) *Anaphylactic shock*, urticaria and angioedema. This syndrome, which may develop to a life threatening situation is usually mediated by specific IgE antibody and so renders the patient vulnerable to further B-lactam antibiotic therapy.

(2) *Hemolytic anemia*. This syndrome is mediated primarily by specific IgG antibody directed against penicilloyl groups on the red blood cell membrane. It is associated only with high dose parenteral therapy.

(3) *Serum sickness* like syndromes comprising rash, fever and arthralgia. These are due to the formation and deposition of antigen-antibody complexes and to the release of inflammatory mediators such as histamine.

(4) *Contact sensitisation*. This is mediated by the presence of specifically sensitised lymphocytes and does not involve serum antibody. Now that topical penicillin treatment is discouraged, contact sensitisation is primarily a problem associated with occupational contact.⁸

In addition to other syndromes which have an immunological basis, penicillins, and in particular the α -amino penicillins may induce a morbiliform rash, the "ampicillin rash". The etiology of this condition remains to be established. At the present time there is no convincing evidence that it is an allergic reaction and it has been suggested that it be classified as a pseudo-allergic reaction pending clarification of the underlying pathogenesis.⁹

Diagnosis

In spite of the wealth of knowledge regarding penicillin allergy, clinical diagnosis can still present considerable difficulty. Subjective and objective investigations should be undertaken although the latter may be inappropriate because of time or convenience.

Subjective investigations

Whilst there are several features which enable an allergic reaction to be distinguished from other adverse effects (Table I), three points are of particular diagnostic significance in the recognition of life threatening anaphylaxis: (a) the time of onset of the reaction in relation to dosing (anaphylactic reactions usually occur within 30 minutes of the first injection in a patient previously sensitised); (b) the nature of any rash observed (urticarial rashes, often characterised by itching, are typical of anaphylaxis, whereas maculopapular rashes are associated with less acute reactions), and (c) the presence of other features of anaphylaxis, namely angioedema, upper or lower airway obstruction, hypotension. All these features, including urticaria, may of course be part of the clinical picture of other conditions too, and this no doubt leads to the

Table I. Characteristics of allergic drug reactions

Prior exposure to the drug or a related chemical should have occurred.

Re-administration of a small amount of the drug should reproduce the symptoms.

Immunochemical specificity. The response should be elicited by structurally related drugs.

No linear dose relationship.

Reactions occur in a minority of patients.

The symptoms should fall into the accepted spectrum of allergic reactions.

The reaction should resolve itself within a few days or often sooner after therapy is terminated.

frequent but unavoidable mis-labelling of patients as "penicillin-allergic". Pseudo-allergic reactions which can mimic anaphylactic reactions can also cause problems. Mention has already been made of the ampicillin rash but two other pseudo-allergic conditions which have been noted are the Jarisch-Herxheimer reaction^{9,10} and the Hoigne syndrome.^{9,11}

In assessing a patient who claims to be penicillin allergic but may require penicillin therapy, points from Table I and those mentioned above can be considered. A history of maculopapular rash, of reactions which do not involve one or more of the features of reactions detailed above as characteristic of anaphylaxis, or of reactions starting hours or days after the commencement of parenteral or oral penicillin all weigh against anaphylactic sensitivity, and indicate that potentially life-threatening reactions are unlikely to follow penicillin administration. However, clinical experience suggests that it is difficult to give firm recommendations, and most clinicians act with caution when

faced by a patient with a history of penicillin allergy. Objective tests can be helpful but they require access to appropriate reagents and for serum antibody assays, laboratory facilities.

Objective tests

The most useful tests are based on the detection of specific IgE antibody, and are therefore only applicable to diagnosis of the rapid onset anaphylactic and urticarial syndromes. These procedures consist of skin tests and immunoassays.

Skin test materials include (a) benzyl penicillin together with the particular penicillin which caused the suspect reaction or is intended to be used for treatment, (b) breakdown products derived from benzyl penicillin, as constituents of the so-called minor determinant mixture and (c) a conjugate prepared from polylysine and benzyl penicillin (penicilloyl polylysine), to present the major determinant. For the penicillin solution, concentrations in the range 10⁻² to 10⁻⁴ molar can be employed, (4 to 0.04 mg/ml). Unfortunately, neither the minor determinant mixture nor penicilloyl polylysine are readily available commercially but they can be prepared using modest facilities.^{12,13}

Several surveys of the efficacy of these skin test materials have been carried out using large groups of history positive penicillin allergies.¹³⁻²¹ Whilst on a group basis the correlation between a positive history and skin test is not always good, it is clear that a positive skin test on a patient with a positive history is diagnostic of a recent immediate type reaction.¹³⁻¹⁵

Immunoassays to detect specific IgE antibody to the major²² and some minor determinants^{23,24} have been developed,

and although useful and safe, are mainly research tools.

A large number of other objective tests have been investigated and details of the methods and their utility are reviewed by Dewdney. None is of help to a busy clinician.

Management of the allergic patient

Treatment of allergic reactions

The treatment and severity of allergic reactions depends on the latent period between drug administration and symptoms. Anaphylactic reactions, as described earlier, require prompt treatment. Adrenaline should be given intramuscularly into the penicillin injection site, if appropriate, and intramuscularly into a nonoccluded extremity. In the case of injected penicillin the use of a tourniquet to delay absorption of the antibiotic is recommended. The patient should be given oxygen and treated with aminophylline for persistent bronchospasm. Tracheostomy may be required for severe upper respiratory blockage. Treatment for the reversal of hypotension should also be initiated. Patients who have had a severe reaction require monitoring for at least 24 hours for delayed reactions, the incidence of which may be reduced by parenteral hydrocortisone. For minor reactions, oral antihistamines may be sufficient.

Late reactions occurring hours or days after parenteral or oral penicillin treatment are usually much less severe, and although adrenaline may be administered, antihistamines, theophylline and β -agonists may suffice. For other allergic manifestations, antibiotic therapy should be stopped and appropriate supportive care given.

Future therapy

For a patient classified as penicillin allergic, future β -lactam therapy depends on (a) the type of previous allergic reaction experienced as mentioned earlier; (b) their present allergic status; (c) an appreciation of the cross-reacting potential of the β -lactam containing family of antibiotics and (d) an appreciation of the pros and cons of desensitisation strategies.

Duration of sensitivity

Once a subject has become allergic to a penicillin it is likely that they will remain in that state for life. However, with time they may become less sensitive and require a larger challenge to initiate an allergic response. As a pointer towards relative sensitivity it has been shown that skin test positivity and specific IgE antibody levels decrease with time after an allergic event, but some subjects are still positive after 10 years or more.^{17,25,26} Therefore, on an individual basis, it is not possible to predict present status. However, several surveys have shown that a subject with a positive history but negative skin tests is much less likely to react on further treatment than if they were skin test positive.^{13,15}

Cross antigenicity

Individual patient variability, in terms of their immune response, precludes any definitive advice regarding the use of non-cross reacting β -lactams. The problem is also compounded by our lack of knowledge in certain areas. Therefore in the absence of a detailed immunological investigation it must be assumed that all

penicillins are contra-indicated for a penicillin allergic individual.

The introduction of cephalosporin antibiotics raised hopes of alternative β -lactam therapy for penicillin allergic patients. However, early studies using animal raised antisera showed that cephalothin and cephaloridine cross reacted with benzyl penicillin,²⁷ probably because of similarities in the side chains of these compounds. Therefore, it is unfortunate that many clinical studies which have demonstrated cross reactivity between penicillins and cephalosporins have only utilised these materials,²⁸⁻³¹ since the situation with other, and particularly the newer third generation cephalosporins, may be different. Indirectly some recent work by Saxon *et al*³² may be significant. Studies with Aztreonam, a member of a new class of β -lactam containing antibiotics known as mono-bactams, showed that it was non-cross-reactive with benzyl penicillin and cephalothin. This result was due in part to the gross differences between the side chains of those compounds, and since many new cephalosporins utilise similar side chains to Aztreonam, this suggests that they may also be non cross-reactive with at least benzyl penicillin. More clinical and immunochemical studies are required to clarify this point.

Desensitisation

For the proven penicillin allergic in need of penicillin therapy, rush desensitisation provides a possible treatment method. This is usually achieved using small incremental doses of the required drug until full therapeutic courses can be administered. Oral³³ and parenteral³⁴⁻³⁶ routes have been employed. Since highly sensitive individuals will respond to very

small amounts of penicillin, caution must be exercised and full medical surveillance provided.

Another procedure involves the use of a monovalent inhibitor, BPO-Flys, prior to and with the penicillin treatment.³⁷ This compound has been used successfully, but has given positive skin test reactions (fore-warning of possible treatment problems in some patients³⁸ and may not be of use for patients allergic to minor determinants.³⁹ It has failed to live up to its early promise.

Overall, even successful desensitisation by these procedures does not achieve long-lasting effect and the procedure would have to be repeated for any subsequent treatment.

In conclusion Penicillin allergy is certainly the most thoroughly investigated drug induced allergy but there are still difficulties in clinical diagnosis. Patients and particularly children who are diagnosed as penicillin allergic should be given a written account of the insensitivity. Details should also be included in their clinical notes in such a form that reasonable judgements can be made on future therapy.

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VALUE OF METHYLENE BLUE EXAMINATION OF DIARRHEAL STOOLS

A fleck of stool is placed in a drop of methylene blue on a slide and examined as a wet mount under a coverslip. The presence of at least 5 cells, which are clearly polymorphonuclear, per high power field in several fields, are considered positive. This is useful test in naturally acquired acute diarrheal illness, requiring minimal equipment and little time.

The presence of PMNs in acute diarrheal stools should lead to consideration of organisms known to produce inflammatory processes, namely, *Campylobacter*, *Shigella*, *Salmonella*, and in some settings, invasive *Escherichia coli*. Their absence should lead to consideration of noninflammatory processes, such as infections with rotavirus, Norwalk agent, enterotoxigenic *E. coli*, and in some settings, cholera.

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